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EXAMINER	
GREENE, JAIME M	

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1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/607,596	WOJNOWSKI ET AL.	
	Examiner	Art Unit	
	Jaime M. Greene	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) *1-18 and 22-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/05, 6/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to papers filed 8/27/07. Claims 1-44 are pending. Claims 1-18 and 20-44 have been withdrawn and claim 19 is under examination on the merits.

Priority

2. Acknowledgment is made of applicant's claim for foreign priority based on application filed in the EPO on 12/28/00, 1/16/01, and 8/16/01. It is noted, however, that applicant has not filed a certified copy of the foreign priority applications as required by 35 U.S.C. 119(b).

Information Disclosure Statement

3. The information disclosure statements (IDS) were filed on 3/7/05 and 6/27/03. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. Please note that duplicate references were crossed out.

Election/Restrictions

4. Applicant's election with traverse of Group VII, claim 19, and SEQ ID NO:112 in the reply filed on 8/27/07 is acknowledged. The traversal is of the restriction between polynucleotides in subparagraphs a, b, and c in claim 1 on the ground(s) that a search for a polynucleotide capable of hybridizing under stringent conditions to a CYP3A5 gene, wherein said polynucleotide has an additional nucleotide at a position

corresponding to positions 27131/27132 of the CYP3A5 gene would identify a polynucleotide having the amino acid sequence of SEQ ID NO: 141 and also would identify a polynucleotide of SEQ ID NO:112.

5. Applicant's arguments with regard to a polynucleotide capable of hybridizing under stringent conditions to a CYP3A5 gene, wherein said polynucleotide has an additional nucleotide at a position corresponding to positions 27131/27132 of the CYP3A5 gene and SEQ ID NO: 112 have been considered and the restriction requirement between these two sequences is withdrawn.

6. However, the specification does not provide any information detailing the relationship between the polynucleotide encoding a polypeptide of SEQ ID NO: 141 and the sequences SEQ ID NO: 112 and a polynucleotide capable of hybridizing under stringent conditions to a CYP3A5 gene, wherein said polynucleotide has an additional nucleotide at a position corresponding to positions 27131/27132 of the CYP3A5 gene, and it is therefore unclear if the sequences are related. Therefore, the restriction between a polynucleotide encoding a polypeptide of SEQ ID NO: 141 and the polynucleotide capable of hybridizing under stringent conditions to a CYP3A5 gene, wherein said polynucleotide has an additional nucleotide at a position corresponding to positions 27131/27132 of the CYP3A5 gene and SEQ ID NO: 112 is maintained.

7. Accordingly, claim 19 and SEQ ID NO: 112 or a polynucleotide capable of hybridizing under stringent conditions to a CYP3A5 gene, wherein said polynucleotide has an additional nucleotide at a position corresponding to positions 27131/27132 of the CYP3A5 gene are under examination on the merits.

8. Claims 1-18 and 20-44 have been withdrawn from further consideration by applicant pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 8/27/07.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

10. Claim 19 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 19 is broadly are drawn to a method of identifying a polymorphism in a CYP3A5 gene by isolating a polynucleotide of SEQ ID NO: 112 or a polynucleotide capable of hybridizing under stringent conditions to a CYP3A5 gene, wherein said polynucleotide has an additional nucleotide at a position corresponding to positions 27131/27132 of the CYP3A5 gene from subgroups of individuals wherein one subgroup has no prevalence for any cancer and further subgroups have a prevalence for any cancer, and identifying a polymorphism by comparing the nucleic acid sequence of said polynucleotide of said one subgroup having no prevalence for any cancer with at least one or more further subgroups having a prevalence for any cancer. In the interest of

brevity, the following analysis will be limited to SEQ ID NO:112, since a polynucleotide capable of hybridizing under stringent conditions to a CYP3A5 gene, wherein said polynucleotide has an additional nucleotide at a position corresponding to positions 27131/27132 of the CYP3A5 gene is considered to be encompassed by the teaching of SEQ ID NO: 112. Therefore, this rejection is applicable to both nucleic acid sequences.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (*United States v. Teletronics Inc*, 8 USPQ2d 1217 (Fed Cir. 1988)). Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986)) and *In re Wands* 8 USPQ2d 1400 (Fed. Cir. 1988)).

The breadth of the claims and nature of the invention

Claim 19 is drawn to a method of identifying a polymorphism in a CYP3A5 gene by isolating a polynucleotide of SEQ ID NO: 112 from subgroups of individuals wherein one subgroup has no prevalence for any cancer and further subgroups have a prevalence for any cancer, and identifying a polymorphism by comparing the nucleic acid sequence of said polynucleotide of said one subgroup having no prevalence for any cancer with at least one or more further subgroups having a prevalence for any cancer.

The nature of the invention not only involves identifying a polymorphism but also associating that polymorphism with prevalence for any cancer. In addition, since the

specification does not specifically define subgroup or individual to only encompass human, the invention involve examining the polymorphism for an association with cancer in all organisms.

Guidance in the Specification and Working Examples

The specification teaches in table 2C a variant Ch-v-017, g.27131-27132insT in the CYP3AG gene that has SEQ ID NO:112 (page 53) and therefore encompasses a polynucleotide capable of hybridizing under stringent conditions to a CYP3A5 gene, wherein said polynucleotide has an additional nucleotide at a position corresponding to positions 27131/27132 of the CYP3A5 gene.

The specification teaches determining CYP3A5 locus sequence diversity in example 2 (page 39). The specification teaches that 4 new variants were identified in the samples, including a variant Ch-v-017 in exon 11, which was found in 9 out of 45 African American samples and in 1 out of 50 Japanese samples.

The specification does not teach identifying the polymorphism in another other human populations. The specification does not teach examining this variant in patients with any form of cancer. The specification does not teach identifying the polymorphism in any organisms other than humans.

The unpredictability of the art, the state of the prior art, level of skill in the art

While the state of the art and level of skill in the art with regard to correlating gene polymorphisms with cancer is high, the level of unpredictability in associating any polymorphism with any particular cancer is even higher. The level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

Regarding the CYP3A5 polymorphism of SEQ ID NO:112, Hustert (cited in IDS: Hustert, et al. Pharmacogenetic 2001; 11:773-779) teaches identifying a CYP2A5*7, g.27131-27123inT polymorphism in nine African American samples (page 776, col 2, paragraph 2). Although other patient populations were studied (e.g. Hustert teaches collecting liver samples from white West Europeans [page 774, col 1, paragraph 2]) Hustert is silent with regard to the presence of this polymorphism in other patient populations.

Regarding CYP3A5 polymorphisms and cancer, Gervasini (Gervasini, et al. BMC Cancer. 2007 Jul 2;7:118) teaches that CYP3A5 is expressed in the liver, stomach, colorectal epithelium and in colorectal cancer tissue (page 2, col 1, paragraph 1). Gervasini teaches examining the association of CYP3A5 polymorphisms and risk for developing major digestive cancers (page 2, col 1, paragraph 2 continued to col 2.). Gervasini teaches that in spite of the presence of CYP3A5 enzyme activities in gut and liver, and of the relevant role of such enzyme activities in carcinogen activation, the results do not support a major link between common CYP3A5 polymorphisms and digestive cancer risk (page 4, col 2, paragraph 3).

Further, regarding making general associations between CYP genes and any cancer Agundez (Agundez , et al. Current Drug Metabolism, 2004, 5, 211-224) presents an overview of the relationships between CYP polymorphisms and cancer risk of human study populations. Agundez summarizes in Table 1 the most recent case controlled studies (caption), which demonstrated, for example, that while polymorphisms in CYP1A1 have been shown to be associated with lung cancer, there was no association

detected in liver or breast cancer (table 1 and caption). Similar results are presented in Table 1 for 8 additional CYP genes. Therefore, even when an association is found between one CYP gene and cancer, it is unpredictable to associate that polymorphism with risk in other types of cancer.

Quantity of Experimentation

The claims are broadly drawn to associating a CYP3A5 polymorphism of SEQ ID NO:112 and cancer in any subgroups. The specification teaches that the polymorphism is only found in the African American and Japanese populations studied. The specification specifically teaches that the insertion polymorphism was not identified in Caucasian populations. Hustert only teaches identifying the polymorphism in African American populations. Therefore the skilled artisan would be required to perform a large study in order to determine if the polymorphism is present in any other human populations. This would require undue and unpredictable experimentation with no expectation of success, since the specification clearly indicates that the insertion polymorphism was not found in Caucasian. It would be unpredictable that the skilled artisan could apply this method to populations which were not found to contain the polymorphism.

The claims are broadly drawn to associating a CYP3A5 polymorphism of SEQ ID NO:112 and cancer in any subgroups, which includes any organism. The specification does not teach examining this polymorphism in any organism other than humans. The claims encompass any human, dog, cat and gorilla, for example. The specification does not provide any analysis in these other organisms encompassed by the claims.

Therefore the skilled artisan would be required to perform a large study in order to determine if the polymorphism is present in any other organisms and whether this polymorphism is predictably associated with any cancer. This would require undue and unpredictable experimentation with no expectation of success.

The claims are broadly drawn to associating a CYP3A5 polymorphism of SEQ ID NO:112 with any cancer. The specification is silent with regard to associating this polymorphism with cancer. The specification fails to provide any analysis of the insertion polymorphism and any cancer. Without a reasonable expectation that the polymorphism is associated with any cancer, there would be no expectation of success that the experimentation would constitute undue trial and error experimentation. Further, Gervasini teaches that there was no association found between common CYP3A5 polymorphisms and digestive cancer risk. Agundez teaches that several CYP genes, while being associated with some cancers, are not necessarily associated with all cancers. Therefore the skilled artisan would be required to perform a large study using patients with a variety of cancers in order to determine if the CYP3A5 polymorphism of SEQ ID NO:112 can be associated with all cancers. This would require undue and unpredictable experimentation with no expectation of success.

Conclusion

Given the lack of data demonstrating the CYP3A5 polymorphism of SEQ ID NO: 112 in all human populations, the lack of any data correlating the polymorphism with cancer and the lack of data regarding the polymorphism in organisms other than

humans, a method of identifying a polymorphism in a CYP3A5 gene by isolating a polynucleotide of SEQ ID NO: 112 from subgroups of individuals wherein one subgroup has no prevalence for any cancer and further subgroups have a prevalence for any cancer, and identifying a polymorphism by comparing the nucleic acid sequence of said polynucleotide of said one subgroup having no prevalence for any cancer with at least one or more further subgroups having a prevalence for any cancer is replete with unpredictable experimentation that is considered undue.

Thus given the broad claims in an art whose nature is unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the methods of the claims as broadly written.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Levitt (Levitt. International Patent Application Number WO9515400, published 6/8/95).

Levitt teaches that figure 7 provides a listing of markers which can be used to design primers that will direct PCR amplification of the marker (page 14, lines 6-10), and in Figure, 7I-2, Levitt teaches a primer that has 100% homology with SEQ ID NO:112. Since SEQ ID NO:112 is homologous to the primer of Levitt, and since the primers are used for amplification, the primer of Levitt is used to isolate a polynucleotide having SEQ ID NO: 112. Therefore, Levitt teaches isolating a polynucleotide having SEQ ID NO:112 and thereby Levitt also teaches a polynucleotide capable of hybridizing under stringent conditions to a CYP3A5 gene, wherein said polynucleotide has an additional nucleotide at a position corresponding to positions 27131/27132 of the CYP3A5 gene. In the interest of brevity, for the remainder of this rejection, reference will be limited to SEQ ID NO:112, although the reference is considered to apply to both nucleic acid sequences.

Levitt does not explicitly teach isolating the nucleic acid sequence from subgroups of individuals having a prevalence for cancer and having no a prevalence for cancer and comparing the results from the two groups to identify a polymorphism.

However, Levitt teaches the combined analysis of multiple markers using the Applied Biosystems 373 sequencer, which could be used for a linkage study (page 31, lines 3-5). Levitt also teaches that typical linkage study would include about 100 families or about 500 individuals, that for a 5-year study including about 300 markers, approximately 180 gels, or about 3 gels per month, will be required, and that by using the method of this invention, at least 2 gels per day can be run per 373 sequencer.

Levitt teaches that thus, up to 12 investigators can be accommodated on one instrument, which substantially reduces the cost per investigator (page 31, lines 3-10). Levitt teaches that PCR using primer pairs which direct amplification of a DNA segment including one of these loci (markers) can be used diagnostically where the rearrangement associated with the disease causes a change in the length of the PCR product (page 31, lines 17-20). Levitt teaches the loci of many such rearrangements are known and associated with many diseases, especially cancers (page 31, lines 16-17).

Therefore, implicit in the suggested linkage study and the mention of associating loci with cancer is both the comparison of groups of unaffected versus affected patients and performing the study as a linkage study cancer for cancer.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the primers for looking at markers of cancer as part of a linkage study, as implied and taught by Levitt.

One of ordinary skill in the art at the time the invention was made would be motivated to perform a linkage study using the described primers in order to identify markers that could be used diagnostically.

There is a reasonable expectation of success because Levitt both teaches markers that are amplified with the primer that includes SEQ ID NO: 112 and suggests linkage studies and that loci can be associated with cancer; thereby implying that such a study is possible.

Sequence Alignment with Primer A (Group 9, set B) for marker D21S261, Fig 7I-2 (Qy = SEQ ID NO: 112).

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Qy          1 CACCTTACCTA 11

              ||||||||||||

Db          5 CACCTTACCTA 15
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Conclusion

None of the claims have been allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jaime M. Greene whose telephone number is 571-270-3052. The examiner can normally be reached on Monday-Thursday, 7:30am-5:00pm, ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jaime Meredith Greene 10/10/07

JEANINE A. GOLDBERG
PRIMARY EXAMINER
10/15/07